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Martino, Enrico De; Petrini, Laura; Schabrun, Siobhan; Graven-Nielsen, Thomas

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CORTICAL SOMATOSENSORY EXCITABILITY IS MODULATED IN
RESPONSE TO SEVERAL DAYS OF MUSCLE SORENESS

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Highlights

- Muscle soreness provokes neuroplastic changes in cortical sensory excitability
- The neurophysiological changes depend on how excessive the pain sensitization is.
- This model may be relevant for understanding prolonged pain neural adaptation.

ACCEPTED MANUSCRIPT

CORTICAL SOMATOSENSORY EXCITABILITY IS MODULATED IN RESPONSE TO SEVERAL DAYS OF MUSCLE SORENESS

Enrico DE MARTINO¹, Laura PETRINI¹, Siobhan SCHABRUN², Thomas GRAVEN-NIELSEN¹

¹ Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University.

² Brain Rehabilitation and Neuroplasticity Unit (BRAiN-u), Western Sydney University, School of Science and Health, Sydney, Australia

Key words: Persistent muscle soreness, neuroplasticity, cortical somatosensory excitability

Corresponding author:

Professor Thomas Graven-Nielsen, DMSc, Ph.D.

Center for Neuroplasticity and Pain (CNAP)

SMI, Department of Health Science and Technology

Faculty of Medicine

Aalborg University

Fredrik Bajers Vej 7D-3

9220 Aalborg E, Denmark

Phone: +45 9940 9832

Fax: +45 9815 4008

<http://www.cnap.hst.aau.dk/~tgn>

E-mail: tgn@hst.aau.dk

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ABSTRACT

Changes in excitability of the sensorimotor cortex have been demonstrated in clinical musculoskeletal pain although the timing is unknown. Eccentric exercise provokes delayed onset muscle soreness providing a model to study the temporal profile of sensorimotor cortical plasticity during progressively developing muscle soreness. Twelve healthy subjects performed eccentric exercise of the wrist extensors. Likert pain scores, pressure pain thresholds (PPTs) at the extensor carpi radialis (ECR) muscle, somatosensory evoked potentials from electrical stimulation of the radial nerve, maximal wrist extension force, and ECR motor evoked potentials (MEPs) to transcranial magnetic stimulation were recorded before (Baseline), 2-h (2-h Post), 2-days (Day2), and 6-days (Day6) after exercise. Compared with Baseline: 1) Likert pain score was increased 2-h Post and increased further at Day2 ($P<0.01$). 2) ECR PPTs were decreased at Day2 ($P<0.001$). 3) The P45 amplitude of the somatosensory evoked potential from central-parietal recording sites was increased at Day2 ($P<0.001$). 4) Maximal wrist extension force was reduced 2-h Post and at Day2 ($P<0.002$). 5) The cortical area from which ECR MEPs could be elicited was reduced at 2-h Post and at Day2 ($P<0.03$). A reduction in ECR PPTs was correlated ($P<0.027$) with an increase in the P45 amplitude at a centro-parietal recording site.

Perspective: These novel data demonstrate that the somatosensory cortical excitability may be affected by muscle soreness developing over days in parallel with a deficit in the motor system. Cortical neuroplasticity may thus develop in the subacute phase and be relevant for understanding neural adaptation in the transition from acute to persistent pain.

Introduction

Maladaptive neuroplasticity has been documented in the sensorimotor cortex of people with chronic musculoskeletal pain [13] and is suggested to be an important component of the transition from acute to chronic pain [21]. For instance, increased cortical activity and a medial shift of the cortical representation of the back, interpreted as an expansion of the back's representation into the foot and leg area, has been shown in people with chronic low back pain using magnetoencephalography [13]. In another study tactile stimulation on the back of low back pain patients demonstrated a shift in the locus of primary somatosensory cortical activation compared with low back pain patients with less pain intensity [24]. Moreover, the primary motor cortex representation of the back muscles is shifted posteriorly and displays greater overlap in chronic low back pain using transcranial magnetic stimulation (TMS) [49,50,54,55]. Similar sensorimotor cortical adaptations have also been reported in chronic lateral epicondylalgia [4, 44], rotator cuff tears [3], anterior cruciate ligament instability [17] and patello-femoral pain syndrome [32, 52] indicating altered corticospinal drive to muscles associated with the painful/damaged structure.

Short-term experimental muscle pain models in healthy individuals have been used to study the effect of acute nociception on sensory [37, 38, 45] and motor cortical excitability [34, 51]. These acute experimental pain models have revealed altered sensorimotor cortical excitability, based on somatosensory evoked potentials (SEPs) [37, 38, 45], motor evoked potentials (MEPs) [34, 51] and intra-cortical inhibition and facilitation [43]. Contrary to the predominantly inhibitory effect of acute pain on sensorimotor cortical excitability, increased excitability and enlarged cortical areas of the primary motor cortical representation have been described after several days of experimental muscle soreness [42]. Such findings suggest the response of the motor cortex differs between long-lasting muscle hyperalgesia compared with acute short-lasting muscle pain.

To date, no study has investigated the adaptation of sensory cortical excitability across several days of muscle soreness. Although clinical studies have shown enhanced cortical responses to innocuous and painful somatosensory stimuli in patients affected by chronic musculoskeletal pain [10, 13, 15, 24], acute short-lasting muscle pain has shown a depression of the excitability of the somatosensory cortex, explained by pain-induced cortical gating of afferent inputs [37,45]. Consequently, the effect of muscle soreness on sensory cortical excitability may potentially develop over time in the absence of short-lasting muscle pain although the specific timing is unknown.

The purpose of this study was to assess changes in sensorimotor cortical excitability during experimental muscle soreness across several days provoked by eccentric exercise of wrist extensors. It was hypothesized that muscle soreness across several days would result in i) increased sensory cortical excitability, based on somatosensory evoked potentials by means of electrical stimulation of the radial nerve, and ii) increased corticomotor excitability of a wrist extensor muscle, assessed as motor evoked potentials induced by transcranial magnetic stimulation in primary motor cortex.

Methods

Subjects

The recruitment and data collection have been conducted in summer 2016 at Center for Neuroplasticity and Pain (CNAP), Aalborg University (Denmark). Twelve healthy right-handed subjects (6 females) participated in the study, recruited through online advertising and flyers posted at Aalborg University. The age, height, and weight (mean \pm SD) were 24 ± 3.2 years, 167 ± 8.7 cm, and 61 ± 10.7 kg, respectively. Subjects had no history of upper limb pain, spine pain, or

neurological disorders. Before starting experimental procedures subjects completed a transcranial magnetic stimulation (TMS) safety screen and a physical examination was performed to check the presence of full pain free range of elbow and wrist motion, and the absence of tenderness to palpation of the soft tissues in the extensor muscles of the wrist. The study was approved by the local Ethics Committee (N-20160022) and was performed in accordance with the Helsinki Declaration. Written informed consent was obtained prior to study commencement.

Study design

The study comprised 5 identical sessions on 4 different days. At the beginning of each session, pain related questionnaires (muscle soreness intensity, patient-rated tennis elbow evaluation and pain body chart) were evaluated, followed by TMS evaluation (rest motor threshold, motor evoked potentials in the hot spot and TMS motor mapping). TMS procedures took approximately 1 hour. Afterwards, EEG and electrical stimulation settings were prepared, participants were instructed about the test and two blocks of 500 sensory evoked potentials were recorded. EEG procedures took approximately 1 hour. Then, participants performed the max grip force and max wrist extension force and finally pressure pain thresholds were collected. The entire session lasted approximately 3 hours.

The first session on Day-1 (the day before the Baseline session) was defined as a training session and not analysed further. Baseline measures were made on Day0. Immediately following these measures, eccentric exercise of the right wrist extensor muscles was performed to induce muscle soreness (delayed onset muscle soreness) that was expected to peak after 2 days [23]. Two hours after the eccentric exercise protocol a post-exercise session (2-h Post) was performed and on Day2 and Day6 data collection sessions were also repeated.

Muscle soreness

To induce muscle soreness lasting for several days, eccentric-exercise provoking delayed onset muscle soreness (DOMS) of the wrist extensor muscle was induced in accordance with procedures described previously [8, 23, 48]. Briefly, the participant was seated, holding a weight in their right hand, with the forearm pronated. Eccentric contractions of the right arm were performed from maximally extended wrist position to maximally flexed wrist position. One set consisted of five repetitions with a weight corresponding to 90% of the maximal voluntary contraction and sets were separated by rest periods of approximately 1-min.

Muscle soreness and arm disability

The participants were asked to evaluate the quantitative value of subjective muscle soreness at the beginning of each experimental session on a 7-point Likert scale where 0 represented a complete absence of pain/soreness; 1: a light pain/soreness in the muscle felt only when touched/a vague ache; 2: a moderate pain/soreness felt only when touched/a slight persistent ache; 3: a light muscle pain/soreness when lifting objects or carrying objects; 4: a light muscle pain/soreness, stiffness or weakness when moving the wrist or elbow without gripping an object; 5: a moderate muscle pain/soreness, stiffness or weakness when moving the wrist or elbow; and 6: a severe muscle pain/soreness, stiffness or weakness that limits my ability to move [48].

The patient rated tennis elbow evaluation (PRTEE) questionnaire was used to assess average pain and disability of the right arm [25] at the start of each session referring to the 24 hour period prior data collection. Scores for pain (sum of 5 items with maximum total score of 50) and disability (sum of 10 items, divided by 2, with a maximum score of 50) were combined to give a

total score ranging from 0 (no pain and no functional impairment) to 100 (worst pain imaginable with significant functional impairment) [25].

The quality of muscle soreness was assessed using either an English [29] or a Danish version of the McGill Pain Questionnaire (MPQ) [11] to investigate the characteristics of the experimental muscle soreness. Words chosen by at least 30% of participants were reported [48]. Finally, participants were asked to draw the area and distribution of muscle soreness on a standardized diagram of the right arm.

Pressure pain sensitivity

Based on the original pain model [48], pressure pain thresholds (PPTs) were recorded using a handheld algometer (1-cm² probe, Algometer type II, SOMEDIC Electronics, Solna, Sweden) to applied pressure at a rate of 30 kPa/s perpendicular to the skin. The PPT was defined as the point where the perception of pressure changed to a perception of pain [22] and participants were asked to press a button when the sensation of pressure first became painful. Three readings were made at each of 4 sites: 1) right extensor carpi radialis (ECR) muscle, 2) left ECR, 3) right tibialis anterior (TA), and 4) left TA. The interval between each PPT assessment was approximately 30 s. The average PPT of the 3 measures at each site was used for statistical analysis.

Grip force

Participants were positioned with their right forearm in a neutral position and 45 degrees elbow flexion. Three maximal voluntary grip forces with strong verbal encouragement were recorded with a custom-made grip dynamometer, consisting of a strain gauge (CCT Transducers, Turin, Italy) interposed between two padded bars [2]. Participants gradually increased the force to a maximum

within 5-s. Each maximal contraction was separated by 1 minute to limit possible effects of fatigue. The force signal was sampled at 500 Hz and the maximal grip force among the three contractions was used for statistical analysis.

Wrist extension force

Participants were seated with their right elbow positioned in pronation and 90 degrees flexion. Isometric wrist extension force was recorded via a force sensor (MC3A 250, AMTI, Watertown, MA 02472-4800, USA) mounted above the hand. Three maximal voluntary contractions (MVC) with strong verbal encouragement were performed to record the force exerted during the wrist extension contractions. The contraction force was gradually increased to a maximum within 5-s and each trial was separated by 1 min to limit possible effects of fatigue. The force signal was sampled at 500 Hz and the maximal wrist extension force among the three trials was used for statistical analysis.

Somatosensory evoked potentials

To evaluate the functional excitability of the somatosensory cortex, somatosensory evoked potentials (SEPs) were recorded. According to standardized procedures [7], each subject rested comfortably on a chair in a quiet room when acquiring SEPs. An electrode cap including 124 electrodes was used (g.GAMMA cap², Schiedlberg, Austria) where the F3, F1, Fc3, Fc1, C3, C1, Cp3, Cp1, P3 and P1 scalp sites were used and referred to the contralateral earlobe [33]. The cap was mounted according to 10-5 system with Cz orientated to the vertex of the head [33]. An additional electro-oculogram electrode (Fz1) was recorded superior to the left eye to monitor eye-related movements. The ground electrode in the cap was placed half way between the eyebrows.

Electrode impedance was maintained below 5 k Ω during the data collection. Electroencephalographic signals were amplified (50000x), band-pass filtered (0.1-1000Hz), and sampled at 2400 Hz (g.Hlamp biosignal amplifier; g.tec-medical engineering GmbH, Schiedlberg, Austria).

SEPs were recorded in response to stimulation of the right superficial branch of radial nerve at the wrist. The cathode was placed on the right radial styloid process and the anode two cm proximal (Model 895340, Axelgaard, Fallbrook, CA, USA). A constant current stimulator (NoxiTest IES 230, NoxiTest, Aalborg, Denmark) was used to deliver electrical stimuli of 1 ms duration at a rate of 2 Hz. A 20% variance was incorporated into the stimulus frequency to avoid accommodation. Stimulus intensity was set at three times the perceptual threshold detected in each session. This intensity was considered comfortable by all participants. Two blocks of 500 stimuli were recorded, filtered off-line at 5-500Hz and all traces were visually inspected for artefacts (blinks, eye movements or contraction of scalp musculature) and any contaminated epochs were eliminated before averaging. The artefact-free waveforms were averaged and the peaks P14, N18, P22, N30, P45 and N60 in the frontal leads and P14, N20, P25, N33, P45 and N60 in the parietal traces [58] were identified (Fig. 1), normalised to the pre-stimulation interval (subtracting the mean amplitude in the interval from -100 ms to -20 ms before the electrical stimulation) and the amplitudes and latencies were extracted. For each session and for relevant peaks, the average amplitude across subjects at each recording site was linearly interpolated to generate the SEP maps for illustration of group effects.

Motor evoked potentials and motor map

To evaluate the functional organization of the corticomotor system, motor evoked potentials (MEPs) to transcranial magnetic stimulation were recorded [39]. All TMS procedures adhered to the TMS checklist for methodological quality [6]. Participants were comfortably seated and instructed to maintain their hand and forearm relaxed, supported by a desk, with the wrist pronated throughout the experiment. TMS was applied (Magstim 200, Magstim Co. Ltd, Dyfed, UK) with a figure-of-eight shaped coil (7 cm external wing diameter). With a swimming cap marked with a 1×1 cm grid (stimulation grid) and orientated to the vertex of the head (point 0, 0 of the grid was the interception between nasion-inion and the inter-aural lines), the coil was positioned over the left hemisphere at a 45-degree angle to the sagittal plane to induce current in a posterior-to-anterior direction. Motor evoked potentials (MEPs) were recorded using surface disposable silver/silver chloride adhesive recording electrodes (Ambu Neuroline 720) positioned over the right ECR muscle belly in parallel with muscle fibres. MEP signals were band-pass filtered at 5 Hz-1 kHz and sampled at 2 kHz. Data were digitized by a 16-bit data-acquisition card (National Instruments, NI6122) and saved by custom-made Labview software (Mr. Kick, Aalborg University).

To evoke responses in the right ECR muscle, the optimal cortical site (hotspot) was determined as the coil position that provoked a maximal peak-to-peak MEP for a given stimulation intensity. Two measures were collected at the hotspot: 1) Resting motor threshold (rMT), defined as the minimum stimulation intensity at which 5 out of 10 stimuli applied at the hotspot evoked a response with a peak-to-peak amplitude of a minimum 50 μ V [39]. 2) Based on the MEPs of 10 stimuli at 120% of rMT at the hotspot site, the peak-to-peak amplitudes were extracted and averaged for analysis [42].

Using a TMS intensity of 120% rMT, motor cortical maps were established based on MEPs evoked every 6 s, in order to avoid any neuromodulatory effects [5], with a total of 5 stimuli at

each site on the stimulation grid [46]. Grid sites were pseudo randomly stimulated from the hotspot until no MEP was recorded (defined as <50- μ V peak-to-peak amplitude) in all five stimuli at all border sites [46]. Trials containing background EMG activity were discarded (pre-stimulation activity > 10 μ V). The number of active map sites (map area) and map volume were calculated off-line. If the average peak-to-peak amplitude of the 5 MEPs evoked at that site was greater than 50 μ V, the site was considered “active” [46]. The averaged peak-to-peak MEP amplitudes at all active sites were summed to estimate the map volume. The centre of gravity (CoG) was defined as the amplitude-weighted centre of the map [60] and was calculated by $\frac{\sum V_i \cdot X_i}{\sum V_i}$; $\frac{\sum V_i \cdot Y_i}{\sum V_i}$; where V_i represents mean MEP amplitude at each site with the coordinates X_i , Y_i [57]. Finally, the number of discrete peaks in the map, defined as the number of grid sites over which TMS evoked a discrete “peak” in the motor cortex representation, was determined. For this, motor cortical map was normalised to the maximum MEP amplitude of the map for each session. Discrete peaks were identified if i) the MEP amplitude at a grid site was greater than 50% of maximum, and if ii) it was separated by a reduction in amplitude of at least 5% of peak MEP amplitude (normalized) in 7 out of 8 of the surrounding grid sites, and finally if iii) it was separated by at least 1 grid site from another peak that satisfied the first 2 criteria procedure [42]. For each session the average peak-to-peak MEP amplitude at all sites across subjects were linearly interpolated to generate the MEP maps used for illustration of group effects.

Statistics

All data in text and tables are presented as mean and standard deviations (SD). Statistical analyses were performed using Stata (v14.0). Statistical significance was set at $P < 0.05$. First, to test for normality, all data were assessed using Shapiro-Wilk normality test. Normal distributed data were

tested using a parametric one and two-way repeated measures analysis of variance (ANOVA), and non-normal distributed data were tested with Friedman analysis of variance and Wilcoxon signed-rank test. Investigating the effects of DOMS, repeated-measures ANOVAs were performed to analyse the dependent measures (clinical and neurophysiological measures) measured repeatedly over several Days (four time points). Therefore, two-way repeated-measures ANOVA with *Days* (Baseline, 2-h Post, Day2 and Day6) and *Side* (right and left) as within subject factors were performed on PPTs for the ECR and TA muscles, respectively. To investigate the changes in maximal force measures (grip force and maximal wrist extension force) and neurophysiological data (rMT, MEP, MEP active sites, MEP map volume, MEP discrete map peaks, MEP CoG, and SEP amplitude, and SEP latency) over Days, one-way repeated-measures ANOVA was applied to compare changes between Days (Baseline, 2-h Post, Day2 and Day6). Ordinal categorical variables (7-point Likert scale and PRTEE) were analysed using non-parametric tests (Friedman test) over Days (Baseline, 2-h Post, Day2 and Day6). To compensate for the use of multiple ANOVAs in the analysis of EEG data (10 recording sites) the P-value from the ANOVAs was Bonferroni corrected to $P < 0.005$ (i.e. $0.05/10$) for accepting significance. In case of significant factors, post-hoc analyses were performed using Bonferroni multiple comparison tests or Wilcoxon signed rank test (Bonferroni corrected). To investigate whether sensory and motor outcomes (PPT and maximal force) correlates with neurophysiological outcomes (rMT, MEP, number of active MEP sites, MEP map volume, MEP discrete number of map peaks, MEP CoG, SEP amplitude, and latency of SEP), Pearson's correlation or Spearman's rank correlation analyses were performed on percentage change relative to Baseline extracted for all sessions. Only significant changes over time in both clinical and neurophysiological outcomes were considered for correlation.

Results

Pain and self-reports

Subjects completed between 50 and 130 eccentric contractions (87 ± 30) before the force dropped by 50% of the MVC. Likert scale scores of subjective muscle soreness were increased (Friedman = 33.69; $P < 0.001$) at 2-h Post (2.5 ± 1.5) compared with Baseline (0 ± 0) and increased further at Day2 (3.9 ± 1.2 ; $P = 0.013$) and then decreased at Day6 (0.3 ± 0.5 ; $P < 0.001$) compared with 2-h Post. At Day2, 11 of 12 subjects reported 2 or more on the Likert scale and 1 subject scored 1 and at Day6, 3 of 12 subjects reported 1 on the Likert scale. The PRTEE total scores increased (Friedman = 32.12; $P < 0.001$) at Day2 (25.1 ± 15.9) compared with Baseline (0 ± 0) and then decreased at Day6 (1.4 ± 4.1 ; $P < 0.001$).

Two hours after the eccentric exercise (2-h Post), participants reported muscle soreness mainly located in the radial side of the right forearm (Fig. 2). The area of muscle soreness increased at Day2 and then decreased at Day6. One participant indicated referred muscle soreness to the triceps region at Day2.

On the McGill Pain questionnaire, participants described muscle soreness at Post as sore (33% of subjects), tugging (33%), tiring (33%). Participants described the muscle soreness at Day2 as taut (42%), annoying (42%), dull (33%), tight (33%), pressing (33%) and sore (33%).

Pressure pain sensitivity

The ANOVA of PPTs measured over the ECR muscles indicated an interaction between factors Days and Side (ANOVA: $F = 18.39$; $P < 0.001$) demonstrating reduced PPTs at the right ECR muscle at Day2 (124.0 ± 77.9 kPa) compared with Baseline (200.0 ± 94.6 kPa, $P < 0.001$), 2-h Post ($177.0 \pm$

95.2 kPa; $P < 0.001$), and Day6 (217.0 ± 124.8 kPa; $P < 0.001$) as well as the control side at day2 (186 ± 99.7 kPa, $P < 0.001$). PTTs measured over the TA muscle were not significantly affected over Days or between Sides (422.2 ± 185.8 kPa across Days and Side; ANOVA: $F = 0.19$; $P = 0.90$).

Grip force

At Baseline the maximal grip force was 33.8 ± 9.8 kg. Compared with Baseline, the maximal grip force was reduced (ANOVA: $F = 15.11$, $P < 0.001$) at 2-h Post (29 ± 7.8 kg, $P = 0.002$) and Day2 (29.4 ± 8.6 kg, $P = 0.002$) and then recovered at Day6 (34.4 ± 11 kg).

Wrist extension force

At Baseline the wrist extension force was 137.3 ± 44 N. Compared with Baseline, the maximal wrist extension force was reduced (ANOVA: $F = 21.67$; $P < 0.001$) at 2-h Post (96.3 ± 36.9 N; $P = 0.002$) and Day2 (114.0 ± 51.4 N, $P = 0.002$) and then recovered at Day6 (145.0 ± 56.2 N).

Sensory evoked potentials

The intensity used to stimulate the radial nerve was 15.0 ± 5.3 mA at Baseline, 14.9 ± 5.4 mA at 2-h Post, 14.8 ± 5.5 mA at Day 2, and 15.3 ± 5.5 mA at Day 6. The average number of artefact-free waveforms used to calculate the SEPs were 658 ± 81 at Baseline, 660 ± 170 at 2-h Post, 611 ± 143 at Day2, and 619 ± 118 at Day 6.

Grand average of SEPs from right radial nerve stimulation is presented in Fig. 3. Significant time effects were found between days for P45 in the centro-parietal recording sites (Table 1) whereas for peaks P22 in the frontal recording sites a strong tendency for time effects was found (Table 2). On P3, P1, Cp3, Cp1 and C1 recording sites, the peak amplitude of P45 increased at Day2

compared with Baseline and 2-h Post (Table 1). On P1, Cp1 and C1, the increase in the amplitude of the P45 peak persisted at Day6 compared with Baseline and 2-h Post. For all recording sites, the peak amplitude of P14 (ANOVA: $F < 3.74$, $P > 0.02$), N18/N20 (ANOVA: $F < 3.12$, $P > 0.39$), N30/33 (ANOVA: $F < 3.03$, $P > 0.043$), and N60 (ANOVA: $F < 1.61$, $P > 0.21$) were not significantly altered at any recording sites over Days (ANOVA P-values Bonferroni corrected due to multiple ANOVAs; i.e. accepted at $P < 0.005$).

Motor evoked potentials and motor maps

The ANOVAs of rMT, MEPs, number of discrete peaks, and position of CoG were not significantly affected over Days (Table 3). The number of active sites (map area) and map volume (Table 3 and Fig. 4) were reduced at 2-h Post and Day2 compared with Baseline ($P = 0.002$ and $P = 0.028$, respectively). The map area was still reduced at Day6 compared with Baseline ($P = 0.026$).

Correlations between force measure, PPT and motor evoked potentials, sensory evoked potentials

Based on 2-h Post, Day2 and Day 6 data (relative to Baseline), a reduction in PPTs (allodynia) in the right ECR muscle was associated with an increase in P45 amplitude at P3 (Spearman $R = -0.367$, $P = 0.027$; Fig. 5A). No significant correlations were found between PPTs in the right ECR and P45 amplitude at P1, Cp3, Cp1 and C1. Interestingly, the changes in wrist extension force and grip force, respectively, were not significantly correlated with the reduction of MEP map volume and map area. Reduction of motor map area and volume, respectively, were not significantly correlated with the increase in P45 amplitude on P3, P1, Cp3, Cp1 and C1.

The changes in Maximal Wrist Extension Force and Maximal Grip Force were correlated with a decrease in PPTs on the right ECR muscle (Pearson $R = 0.475$; $P = 0.003$ and Pearson $R = 0.469$; P

= 0.004, respectively; Fig. 5B, 5C). Finally, a reduction in PPT on the right ECR muscle was correlated with an increase of Likert scale scores (Spearman Rho = -0.574; $P < 0.001$; Fig. 5D).

Discussion

The main purpose of this study was to investigate the effect of muscle soreness, induced across several days, on i) somatosensory cortical excitability, assessed by electrically somatosensory evoked potentials, and ii) corticomotor output, assessed by TMS-induced motor evoked potentials. These data demonstrate for the first time, modulation of somatosensory cortex excitability (increased amplitude of centro-parietal P45) and corticomotor excitability of the representation of ECR (reduced MEP map volume and area) in response to DOMS. These effects were particularly evident when reduction of pressure pain sensitivity peaked 2 days after the exercise protocol. The present findings provide novel insight into the nature and temporal profile of sensorimotor cortex excitability during sustained muscle soreness.

Tonic muscle soreness alters somatosensory cortex excitability

Structural and functional reorganization of somatosensory cortical areas have been well described in chronic musculoskeletal pain patients compared with healthy subjects [13,47], suggesting maladaptive neuroplasticity of somatosensory cortex. Previous studies have also shown altered somatosensory cortex excitability in response to acute discharge of nociceptive inputs [37,38], confirming that acute pain can modulate somatosensory cortex excitability and cause rapid functional reorganization of the somatosensory cortex.

Based on functional magnetic resonance imaging (fMRI), recent studies showed that muscle soreness induced by eccentric exercise disclosed widespread activation in the primary

somatosensory [62] and motor cortices [27,62] during dynamic and static movement-evoked pain, suggesting that muscle soreness induced by exercise provide an effective, non-invasive model to study the central processing of inflammatory muscle pain [62]. The present study is the first to investigate adaptation of the somatosensory cortical excitability across several days of muscle soreness. This is particularly relevant since no longitudinal studies exist, assessing cortical excitability before chronic pain patients present with maladaptive excitability changes. While previous studies using intramuscular injections of algescic substances evoking acute pain showed a rapid reduction of parietal complex N20-P25-N33 during and immediately following pain [37, 38, 45], the present study showed an increase of amplitude of centro-parietal P45, in particular 2 days after exercise when muscle soreness peaked. One possible explanation of this discrepancy can be found in the experimental pain model used in this study. In fact, resting pain is not a typical feature of eccentric exercise-provoking muscle soreness, while injections of algescic substances in the muscle provoke acute short-lasting pain. Because experimental acute muscle pain is strongly accompanied by a reduction of position sense and loss of stimulus perception, Rossi and co-authors suggested that the depression of parietal complex N20-P25-N33 is likely an effect of pain-induced cortical gating of low-threshold afferent inputs [37, 38]. Contrary to this, the absence of resting pain during the electrical stimulation for SEP assessment in the present study could fail to provoke any cortical gating and the changes of cortical reactivity to low-threshold afferent discharge may represent an adaptation of cortical processing of somatosensory afferent information from the sore tissue. In addition, the increased P45 amplitude was correlated with the increased pain sensitivity to mechanical pressure, complementing the information provided by the repeated measurement ANOVA and suggesting that both adaptations could be a consequence of a common cause, but do not necessarily causally related.

Earlier evidence suggests that changes of P45 amplitude can be driven by selective spatial attention [9,14]. Based on these findings, it is possible that, even if the participant were told to be completely relaxed and avoid focusing on the electrical stimulation on the right wrist, muscle soreness on the right forearm may provoke attention changes towards the stimulated territory. However, DOMS is a clinical condition characterized by absence of muscle pain at rest that makes it unlikely that muscle soreness during the SEP assessment caused a change in the spatial attention.

Although the exact origin of SEPs is not fully understood [1,58], cortical-surface recordings and transcortical recordings show that these potentials are generated in parietal and frontal cortex [1,20]. For instance, clinical studies showed that a complete parietal lesion produced hemianaesthesia, without upper motor neurons signs, eliminated the parietal complex N20-P25-P45, while the frontal complex P22-N30 persisted at usual latencies [28], suggesting that the complex N20-P25-P45 involve mainly the parietal region of the scalp. In addition, several studies have also drawn attention to a possible second thalamo-cortical loop that connects the thalamus with the frontal cortex [16,28], suggesting that the frontal complex P22-N30 may have an independent pathway. Since these studies found dissociate alterations of frontal and parietal SEP generators in different physiological condition and neurological diseases, the combined use of the frontal and parietal recording sites referenced to the earlobe in this study were selected to reflect the multiplicity of cortical excitability adaptations provoked by muscle soreness. The main SEP components affected in the present study was centro-parietal P45 (centro-parietal recording sites), suggesting that the parietal cortex was mainly affected by muscle soreness.

Several studies have shown modulation of frontal and parietal SEPs in response to multimodal somatosensory stimulation or non-invasive cortical stimulation. For instance,

attenuation of SEPs has been described during active and passive movement [40], tactile stimulation [20], water immersion [41], passive heat stress conditions [31], 1Hz repetitive TMS [12] and continuous theta burst stimulation [18], whereas enhancement of SEPs has been described in response to motor learning [30], attention [14], anesthetics blocks [53], paired associative stimulation [61] and intermittent theta burst stimulation [19]. These results suggest that the excitability of the sensory cortex can be modulated through several different interventions and a challenge for future research is to use and/or develop different therapeutic interventions able to reverse or modulate sensory cortex adaptations provoked by muscle pain.

The Influence of muscle soreness on corticomotor output

Using electrical stimulation of the motor cortex in patients affected by chronic pain [56] has demonstrated a strong relationship between pain and excitability of the motor cortex. Based on transcranial magnetic stimulation, it has been documented that patients with chronic musculoskeletal pain show several changes in corticospinal and intracortical excitability, such as higher MEP threshold [17,49,50], higher silent period threshold [17,49,50], increased or decreased map volume [44,55], reduced intracortical inhibition [4,26], increased intracortical facilitation [4] and overlap of the CoG of different muscles [44,54], suggesting that chronic pain can modulate motor cortex excitability and cause a dysfunctional reorganization of M1.

When experimentally-induced tonic muscle pain is applied, corticomotor excitability has previously been characterized by a decreased response, evoked by magnetic brain stimulation, in the painful muscle when subjects were at rest [34]. This reduction in excitability has been described both at cortical and spinal level [34]. With muscle soreness lasting for several days after intramuscular injections of nerve growth factor, expansion of the motor map of the affected

muscle has been described [42], suggesting a different corticomotor adaptation during muscle soreness across several days without prior contractions.

In the present study corticomotor excitability of ECR was reduced after eccentric exercise provoking DOMS and, interestingly, it was still depressed after 2 days, even though the metabolic fatigue and changes in the sarcolemmal excitability (M-wave) were presumably recovered [35,36]. Because of the methodology selected for this study, it is not possible to determine the specific level of the changes in the excitability along the motor pathway, however, spinal inhibition during delayed onset muscle soreness (DOMS) has been demonstrated previously [59]. The H-reflex after eccentric exercise of the trapezius muscle was decreased immediately and 24 h after exercise, potentially explained by increased presynaptic inhibition of Ia afferents, likely mediated by the firing of the group III and IV afferents, or an increase in threshold of the Ia axons [59]. Attenuated corticomotor excitability found in the present study may be explained by these peripheral or spinal inhibitory effects provoked by DOMS.

Conclusion

This study shows for the first time that exercise-induced muscle soreness lasting for several days is associated with adaptations of somatosensory evoked potentials generated by centro-parietal cortex and by decreased motor-map area of the affected muscle. These findings provide novel insight into the temporal profile of sensorimotor cortex excitability during sustained muscle soreness that may have relevance for understanding the plasticity of cortical excitability in the transition from acute to subacute pain conditions.

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ACCEPTED MANUSCRIPT

FIGURE LEGENDS

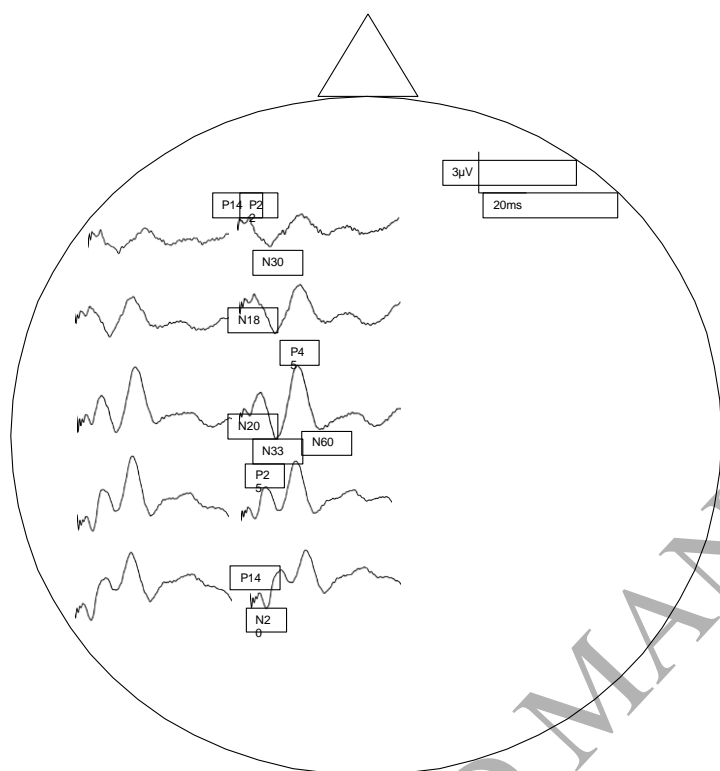


Figure 1: Right radial nerve SEPs recorded by frontal electrodes (F3, F1, Fc3, Fc1) and centro-parietal electrodes (C3, C1, Cp3, Cp1, P3 and P1) scalp sites placed according to the 10-20 system. P14, presented over all the traces, is indicated in the F1 and P1 traces. The N18 and N20 responses are shown in the Fc1 and P1 traces, respectively. P22 and P25 are indicated in F1 and Cp1 and N30 and N33 are labelled in the F1 and C1. Last, P45 and N60, presented over all the traces, are indicated in the C1.

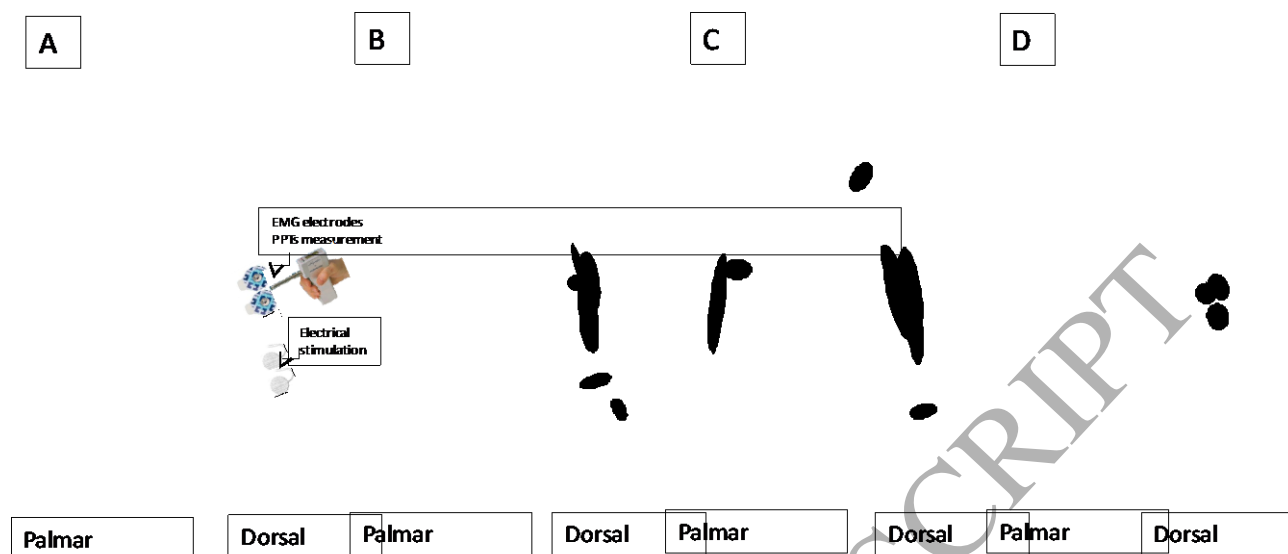


Figure 2: Body chart pain drawings (palmar and dorsal view of the right arm) showing distribution of muscle soreness at Baseline (A), 2-h Post (B), Day2 (C), and Day6 (D). On A is also shown where the PPT of right ECRB and MEP to ECRB were assessed and electrical stimulation was applied for SEP measurement.

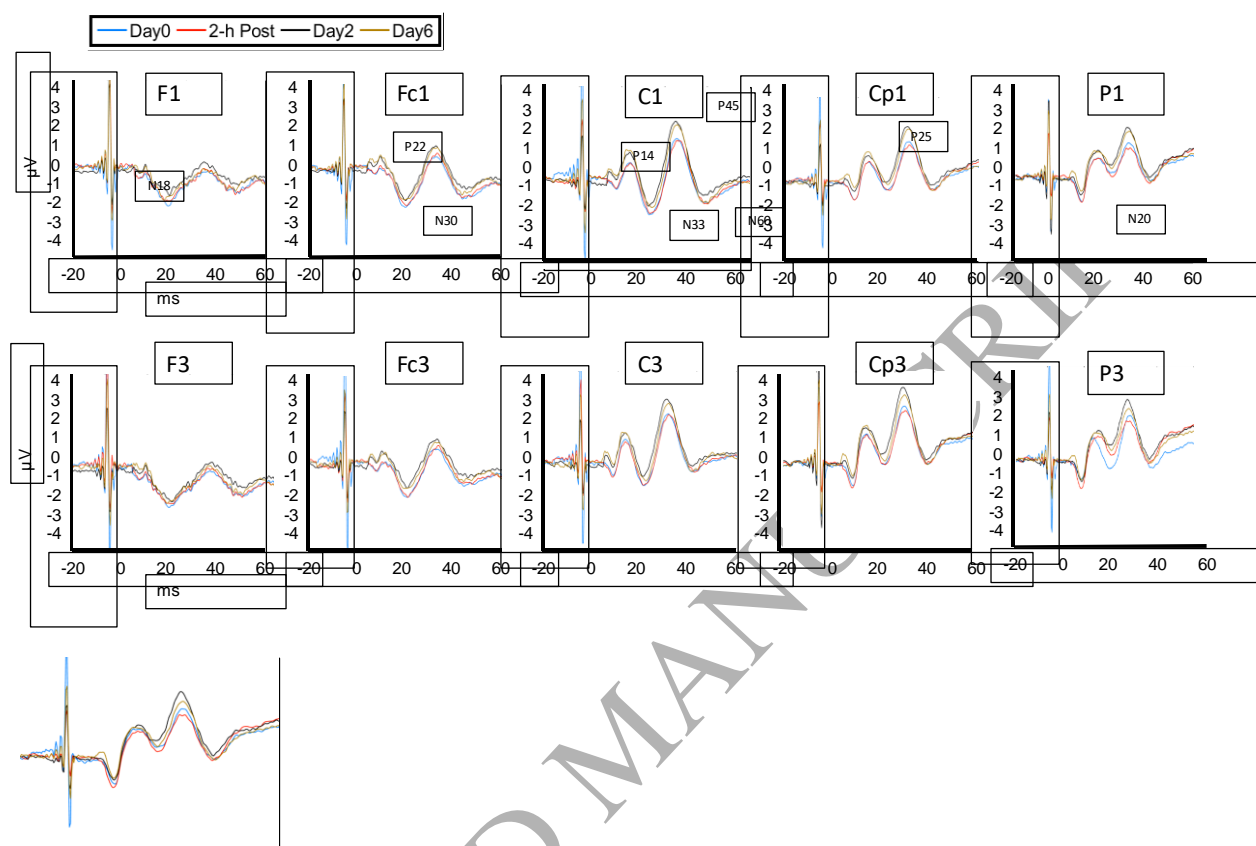


Figure 3: Grand average of SEPs from right radial nerve stimulation recorded by frontal electrodes (F3, F1, Fc3, Fc1) and centro-parietal electrodes (C3, C1, Cp3, Cp1, P3 and P1) scalp sites placed according to the 10-20 system. P14, presented over all the traces, is indicated in the C1 trace. The N18 and N20 responses are shown in the F1 and P1 traces, respectively. P22 and P25 are indicated in Fc1 and Cp1 and N30 and N33 are labelled in the Fc1 and C1. Last, P45 and N60, presented over all the traces, are indicated in the C1.

ECR Motor maps

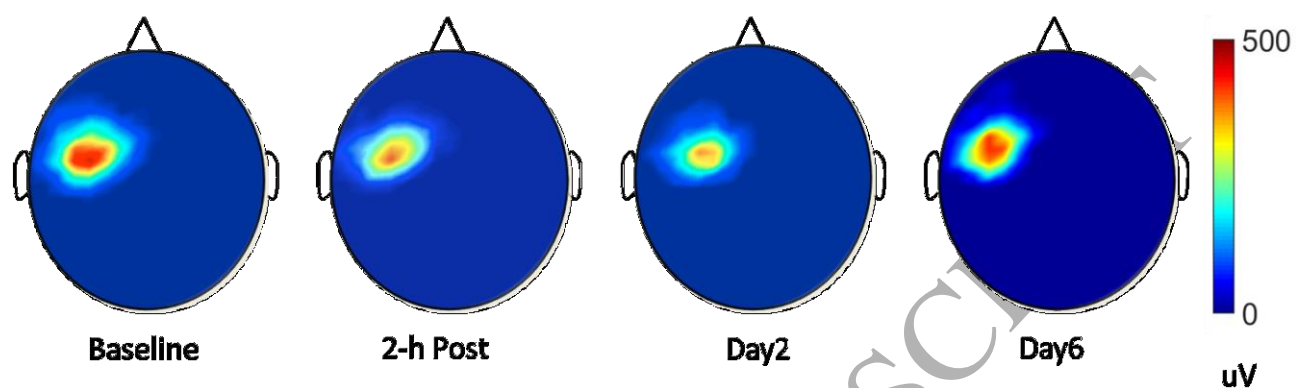


Figure 4: Averaged ($N = 12$) peak-to-peak MEP amplitudes of the right ECR muscle interpolated across stimulation sites at Baseline (before exercise), 2-h Post, Day2 and Day6. The colour scale represents amplitude (from 0 to 500 μV). Note the decrease of map excitability (reduction of map volume and less number of active sites) two hours (2-h Post) and 2 days after the exercise (Day2).

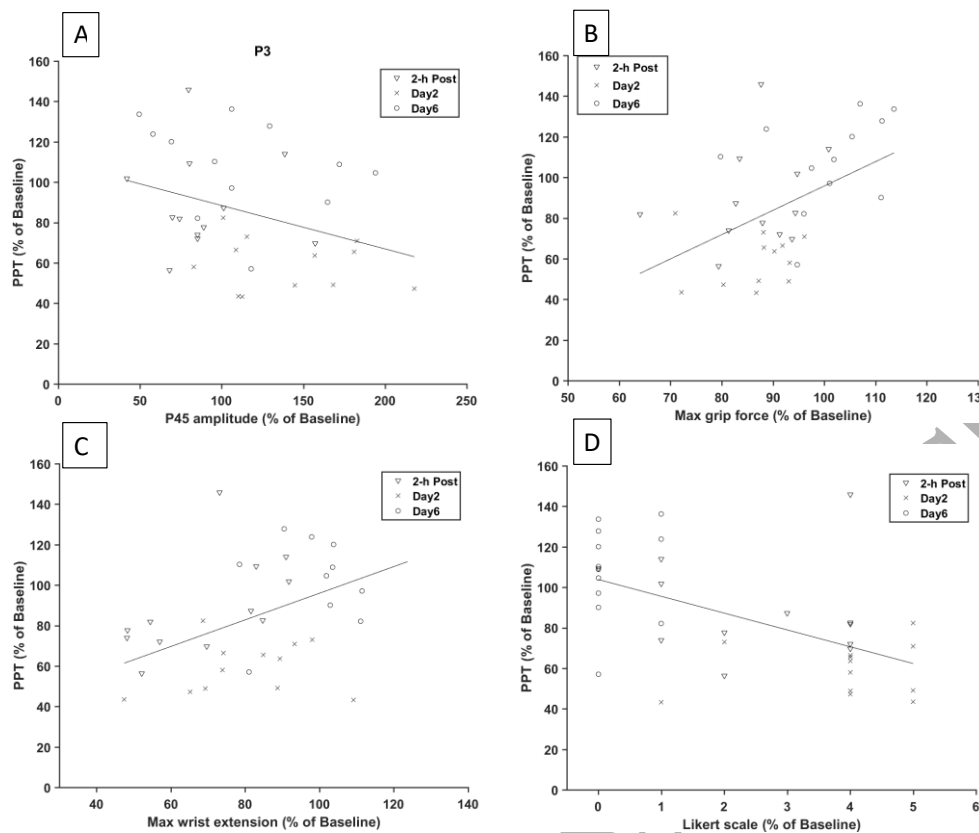


Figure 5: Correlation between PPTs on the right ECR and P45 amplitude on P3 (data expressed as percentage of Baseline, from 2-h Post, Day2 and Day6) (A). Correlation between Maximal Wrist Extension Force and PPTs on the right ECR muscle (data expressed as percentage of Baseline from 2-h Post, Day2 and Day6) (B). Correlation between Maximal Grip Force and PPTs on the right ECR muscle (data expressed as percentage of Baseline, from 2-h Post, Day2 and Day6) (C). Correlation between PPTs on the right ECR muscle and Likert scale (data expressed as percentage of Baseline, from 2-h Post, Day2 and Day6) (D). Linear regression lines were based on all time points.

Table 1: Mean (\pm SD, N = 12) SEP amplitude for P45. F-values and P-values (significance accepted at 0.005 due to multiple ANOVAs) are from the one-way repeated-measures ANOVA. Post-hoc test relative to Baseline (*, $P < 0.05$) or Post ($^{\#}$, $P < 0.05$).

	Peak amplitude P45 (μ V)					
Recording site	Baseline	Post	Day2	Day6	F	P-value
F3	0.33 \pm 0.74	0.35 \pm 0.80	0.71 \pm 0.67	0.44 \pm 0.86	1.56	0.218
F1	0.24 \pm 0.66	0.33 \pm 0.87	0.66 \pm 0.72	0.47 \pm 0.76	2.23	0.102
Fc3	1.00 \pm 0.82	1.05 \pm 0.88	1.55 \pm 0.72	1.27 \pm 1.07	2.20	0.107
Fc1	0.89 \pm 1.10	0.98 \pm 1.16	1.52 \pm 1.22	1.25 \pm 1.20	3.12	0.039
C3	2.27 \pm 1.48	2.19 \pm 1.20	3.04 \pm 1.55	2.71 \pm 1.58	4.01	0.015
C1	2.01 \pm 1.74	1.81 \pm 1.52	2.86 \pm 1.96 $^{* \#}$	2.49 \pm 1.85 $^{\#}$	8.08	<0.001
Cp3	2.54 \pm 1.42	2.37 \pm 1.17	3.48 \pm 1.73 $^{* \#}$	3.02 \pm 1.56	8.56	<0.001
Cp1	1.98 \pm 1.46	1.76 \pm 1.09	2.87 \pm 1.64 $^{* \#}$	2.59 \pm 1.23 $^{* \#}$	11.55	<0.001
P3	2.07 \pm 1.02	1.77 \pm 1.05	2.80 \pm 1.39 $^{* \#}$	2.25 \pm 1.23	8.45	<0.001
P1	1.63 \pm 0.94	1.34 \pm 0.85	2.36 \pm 1.12 $^{* \#}$	2.07 \pm 1.18 $^{\#}$	9.97	<0.001

Table 2: Mean (\pm SD, N = 12) SEP amplitude for P22/25. F-values and P-values (significance accepted at 0.005 due to multiple ANOVAs) are from the one-way repeated-measures ANOVA.

	Peak amplitude P22/P25 (μ V)					
Recording site	Baseline	Post	Day2	Day6	F	P-value
F3	-0.01 \pm 0.54	0.04 \pm 0.35	0.38 \pm 0.59	0.34 \pm 0.86	1.53	0.224
F1	-0.07 \pm 0.50	0.01 \pm 0.36	0.32 \pm 0.43	0.32 \pm 0.69	2.53	0.073
Fc3	0.30 \pm 0.43	0.30 \pm 0.30	0.78 \pm 0.60	0.64 \pm 0.56	4.20	0.012
Fc1	0.28 \pm 0.50	0.38 \pm 0.45	0.84 \pm 0.49	0.79 \pm 0.80	4.82	0.0064
C3	1.18 \pm 1.17	1.09 \pm 1.01	1.59 \pm 1.05	1.56 \pm 1.28	4.07	0.014
C1	1.01 \pm 1.35	1.03 \pm 1.23	1.55 \pm 1.32	1.63 \pm 1.65	4.97	0.0059
Cp3	1.44 \pm 1.12	1.47 \pm 0.93	1.83 \pm 1.03	1.83 \pm 1.52	2.18	0.109
Cp1	1.14 \pm 1.17	1.24 \pm 0.94	1.55 \pm 0.94	1.60 \pm 1.52	2.03	0.128
P3	1.27 \pm 0.77	1.26 \pm 0.72	1.50 \pm 0.71	1.29 \pm 1.29	0.55	0.650
P1	0.97 \pm 0.71	1.04 \pm 0.68	1.35 \pm 0.64	1.24 \pm 1.17	1.65	0.196

Table 3: Mean (\pm SD, N = 12) parameters related with motor-evoked potentials (MEPs). F-values and P-values are from the one-way repeated-measures ANOVA. rMT: resting motor threshold. Post-hoc test relative to Baseline (*P < 0.05).

	Baseline	Post	Day2	Day6	F-value	P-value
rMT (%)	42.7 \pm 7.5	41.7 \pm 7.7	42.3 \pm 7.7	41.8 \pm 7.2	1.81	0.16
MEP amplitude (μ V)	532.3 \pm 202.3	440.7 \pm 232	422 \pm 205.1	455.3 \pm 190.7	1.26	0.3
Map area (active sites)	24 \pm 3.5	19.2 \pm 4.7*	18.8 \pm 3.9*	20.1 \pm 4.6*	7.05	<0.001
Map volume (mV)	7.1 \pm 2.3	5.1 \pm 2*	4.5 \pm 2*	5.5 \pm 2.5	5.84	0.0026
Map discrete peaks (number)	1.6 \pm 0.8	1.9 \pm 0.7	1.4 \pm 0.5	1.9 \pm 1.2	1.16	0.33
CoG longitude (cm)	1.2 \pm 0.9	1.2 \pm 0.6	1.4 \pm 0.7	1.1 \pm 0.7	0.97	0.41
CoG latitude (cm)	5.9 \pm 0.6	6.1 \pm 0.6	6.2 \pm 0.7	6.2 \pm 0.4	1.34	0.27